8. (NEW) A host cell comprising the recombinant expression vector of claim 7.

9. (NEW) A recombinant expression vector comprising the nucleic acid molecule of claim 4.

10. (NEW) A host cell comprising the recombinant expression vector of claim 9.

11. (NEW) A recombinant expression vector comprising the nucleic acid molecule of claim 6.

12. (NEW) A host cell comprising the recombinant expression vector of claim 11..--

RESPONSE

I. Status of the Claims

New claims 7-12 have been added. Claims 1-12 are therefore presently pending in the case. For the convenience of the Examiner, a clean copy of the pending claims is attached hereto as **Exhibit A**. In compliance with 37 C.F.R. § 1.121(c)(1)(ii), a marked up copy of the original claims is attached hereto as **Exhibit B**.

II. Support for the Amended Claims

New claims 7, 9 and 11 have been added to more clearly claim aspects of the invention. Support for these claim can be found throughout the specification as originally filed, with particular support being found at least at page 9, lines 21-26.

New claims 8, 10 and 12 have been added to more clearly claim aspects of the invention. Support for these claim can be found throughout the specification as originally filed, with particular support being found at least at page 9, lines 26-31.

As new claims 7- 12 are fully supported by the specification and claims as originally filed, they do not constitute new matter. Entry therefore is respectfully requested.

III. Rejection of Claims Under 35 U.S.C. § 101

The Action persists in rejecting claims 1-6 and therefore newly dependent claims 7-12, under 35 U.S.C. § 101, allegedly because the claimed invention lacks support by either a specific and substantial asserted utility or a well established utility. Applicants respectfully continue to traverse.

Applicants have presented evidence of multiple utilities in the previous response dated May 22, 2002. In addition, Applicants now present further clear and convincing evidence that those of skill in the art would readily recognize the utility the present invention.

In the Final Office Action, the Examiner seems to be implying that the use of the abbreviation NHPs, for novel human proteins is indicative of a lack of understanding or knowledge on the part of Applicant. Applicants are unaware of any regulation requiring the particular naming of a claimed sequence in order for the sequence to meet the utility requirements. Second, the Examiner also seems to be implying that because Applicants' sequence is novel, it lacks utility. Applicants are unaware of any patent law, patent rule, or ruling from the Supreme Court or the Court of Appeals for the Federal Circuit that supports this untenable position.

The Final Office Action also states that "However, there is no evidence in the specification that any of the claimed nucleic acids are not expressed in a single specific tissue" (page 7, line 5). In the specification it was stated Expression analysis has provided evidence that the "described NHPs can be expressed in human liver, mammary gland, salivary gland, lung carcinoma, and gene trapped human cells" (page 2, lines 9-12). Applicants respectfully submit that the following human tissues were also tested using RT-PCR and were found to be negative for expression of the claimed nucleic acids: fetal brain, prostate, brain, testis, pituitary, thyroid, cerebellum, adrenal gland, spinal cord, pancreas, thymus, spleen, stomach, lymph node, small intestine, bone marrow, colon, trachea, skeletal muscle, lung, heart, kidney, uterus, fetal liver and placenta.

The Action also suggests that the use of the presently claimed polynucleotides, as in DNA chips, would be generic. Further, the Action seems to be requiring Applicants to identify the biological role of the nucleic acid or function of the protein encoded by the presently claimed polynucleotides before the present sequences can be used in gene chip applications that meet the requirements of § 101. Applicants respectfully point out that knowledge of the exact function or role of the presently claimed sequence **is not required** to track expression patterns using a DNA chip. As set forth in Applicants First Response, given the widespread utility of such "gene chip" methods using *public domain* gene

sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. The claimed sequence provides a specific marker of the human genome (see evidence below), and that such specific markers are targets for discovering drugs that are associated with human disease. Thus, those skilled in the art would instantly recognize that the present nucleotide sequence would be an ideal, novel candidate for assessing gene expression using, for example, DNA chips, as the specification details at least on page 4, lines 9-12. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, as well as more recently issued U.S. Patent Nos. 5,837,832, 6,156,501 and 6,261,776. Accordingly, the present sequence has a specific utility in such DNA chip applications. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequence, must also be useful.

Additionally, since only a small percentage of the genome (2-4%) actually encodes exons, which in-turn encode amino acid sequences. Thus, not all human genomic DNA sequences are useful in such gene chip applications, further discounting the Examiner's position that such uses are "generic". Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101. It has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971).

Evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company, Rosetta Inpharmatics, was viewed to have such "real world" value that it was acquired by large pharmaceutical company, Merck & Co., for substantial sums of money (net equity value of the transaction was $620 million). The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions

of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304). The results have been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years).

As further evidence of utility of the presently claimed polynucleotide, although only one is needed to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), is the utility the present nucleotide sequence has a specific utility in determining the genomic structure of the corresponding human chromosome, for example mapping the protein encoding regions, as described in the specification at least at page 6, line 28 through page 7, line 9 and evidenced below. Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of the human chromosome containing the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences (see evidence below). In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence.

Only a minor percentage of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The Applicants respectfully submit that the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the

relevant biological and biochemical arts. For further evidence in support of the Applicants' position, the Board is requested to review, for example, section 3 of Venter *et al.* (*supra at* pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article.

As evidence of the specific utility of the sequences of the present invention in localizing the specific region of the human chromosome and identification of functionally active intron/exon splice junctions is the information provided in **Exhibit C**. A blast analysis using the sequence of the present invention indicates that the exons encoding the sequence of the present invention are included in four different clones which are spread along a region of human chromosome 4, thus clearly one would not simply be able to map the protein encoding regions identified specifically by the sequences of the present invention, without knowing those sequences. The first exon of the sequence of the present invention (base 1-170) is on chromosome 4, contained within region identified by clone AC096743. It is located at positions 48822-48991 of the total 103765 total bases of the clone. The second exon of the sequence of the present invention is in a region of chromosome 4 represented by clone AC112249, it contains base167-323 of SEQ ID NO: 1 at position 66611-66767 of 146551. The third exon (bases 321-573) is contained within a region of chromosome 4 represented by 2 clones that either overlap (which they do) or alternatively this exon may as a result of gene duplication be present in both locations in the genome. Both of these clones contain bases 321-573 of the sequence of the present invention. In clone AC107051 the exon is contained from position 2903-3155 of its total 57025 bases and in clone AC121158 the exon is contained from positions 65034-65286 of a total of 192160 bases. Thus clearly the sequences of the present invention have utility in mapping a gene product to the chromosome and in the identification and biological validation of exon/intron splice junctions that are specific to the expression of gene product.

A additional legal issue also arises, that of due process. As many U.S. patents have issued with less information than that provided in the current application. Issued U.S. patents are *legally presumed* to be in full compliance with the provisions of 35 USC sections 101, 102, 103, and 112. Applicants respectfully submit that, absent a change in the law as enacted by Congress and signed by the President, it is improper for the Examiner to hold Applicants' invention to a different legal standard of patentability.

Given the rapid pace of development in the biotechnology arts, it is difficult for the Applicants to understand how an invention fully disclosed and free of prior at the time the present application was filed, could somehow retain *less* utility and be *less* enabled than inventions in issued U.S. patents (which were filed during a time when the level of skill in the art was clearly lower). Simply put, Applicants invention is *more* enabled and retains *at least as much* utility as the inventions described in the claims of many issued U.S. patents. Any argument to the contrary is at best arbitrary and at worst capricious. Absent authority provided by an act of Congress or Executive order, arbitrary or capricious conduct by an administrative office the U.S. government has historically proven to conflict with the provisions of the U.S. Constitution. The Patent Office does not have the authority to rewrite U.S. law. However, the Patent Office does have a Constitutional obligation to administer U.S. law in an unbiased and procedurally consistent manner. That is what the Applicants are respectfully requesting from the Examiner in the present matter.

For each of the foregoing reasons, Applicants submit that in light of the above discussion and those presented in Paper No. 12, the presently claimed nucleic acid molecules have been shown to have a substantial, specific, credible and well-established utility, the rejection of claims 1-5 under 35 U.S.C. § 101 has been avoided, and respectfully request that the rejection be withdrawn.

Those of skill in the art would clearly recognize the utility of the present invention as well as be enabled to make and use the present invention without undue experimentation. Thus, the present invention clearly has credible and well established utility. In light of the evidence presented above and in previous responses, Applicants respectfully submit that the present invention is in full compliance with the provisions of 35 U.S.C. § 101, and respectfully request that the rejection be withdrawn.

IV. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

The Action rejects claims 1-6 and thus newly dependent claims 7-12 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the claimed invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse. Applicants submit that claims 1-6 and thus newly dependent claims 7-12 have been shown to have "a specific, substantial, and credible utility", as detailed in section above. Applicants therefore request that the rejection of claims 1-12 under 35 U.S.C. § 112, first paragraph, be withdrawn.

V. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Myers have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

February 13, 2003
Date

Lance K Ishimoto Reg. No. 41,866

LEXICON GENETICS INCORPORATED
(281) 863-3333

24231
PATENT TRADEMARK OFFICE

Exhibit B

Marked Up Version of Amended Claims in U.S. Patent Application Ser. No. 09/641,831

1. (Amended) An isolated nucleic acid molecule comprising the nucleotide sequence described in SEQ ID NO:1.

2. (Amended). An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO: 2; and

(b) hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 1 or the complement thereof.

3. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence described in SEQ ID NO:3.

4. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO: 4; and

(b) hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 3 or the complement thereof.

5. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence described in SEQ ID NO:5.

6. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO: 6; and

(b) hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 5 or the complement thereof.

7. (NEW) A recombinant expression vector comprising the nucleic acid molecule of claim 2.

8. (NEW) A host cell comprising the recombinant expression vector of claim 7.

9. (NEW) A recombinant expression vector comprising the nucleic acid molecule of claim 4.

10. (NEW) A host cell comprising the recombinant expression vector of claim 9.

11. (NEW) A recombinant expression vector comprising the nucleic acid molecule of claim 6.

12. (NEW) A host cell comprising the recombinant expression vector of claim 11.